PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification [6] :
C07D 307/80, 333/16, 333/56, 263/32, A61K 31/34, 31/38, 31/42

A1

(11) International Publication Number: WO 99/58520

(43) International Publication Date: 18 November 1999 (18.11.99)

(21) International Application Number: PCT/US99/10213

(22) International Filing Date: 10 May 1999 (10.05.99)

(30) Priority Data:
09/076,597 12 May 1998 (12.05.98) US

(71) Applicant: AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940–0874 (US).

(72) Inventors: MALAMAS, Michael, Sotirios; 2443 Oleander Circle, Jamison, PA 18929 (US). ADEBAYO, Folake, Oluwemimo; 216 Dorchester Drive, Cranbury, NJ 08512 (US). DOLLINGS, Paul, Jeffrey; 1012 Eagle Road, Newtown, PA 18940 (US).

(74) Agents: MILOWSKY, Arnold, S.; American Home Products Corporation, Patent Law Dept.–2B, One Campus Drive, Parsippany, NJ 07054 (US) et al.

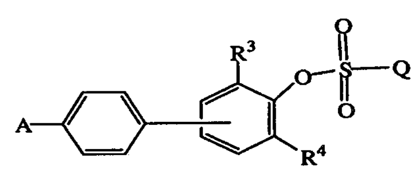
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

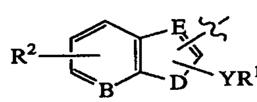
Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

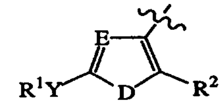
(54) Title: BIPHENYL SULFONYL ARYL CARBOXYLIC ACIDS USEFUL IN THE TREATMENT OF INSULIN RESISTANCE AND HYPERGLYCEMIA

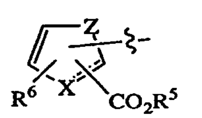
(57) Abstract

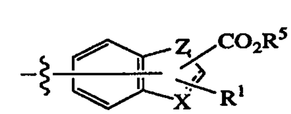
This invention provides compounds of Formula (I) having the structure wherein A is (a) or (b), Q is (c) or (d); B is carbon or nitrogen; D is oxygen, sulfur, or nitrogen; E is carbon or nitrogen; X is carbon, nitrogen, oxygen, or sulfur; Y is a bond, methylene, C(O), or CH(OH); Z is CH=CH, nitrogen, oxygen, or sulfur; the dashed line of Q represents an optional double bond; R^1 is alkyl of 1 to 12 carbons, aryl of 6–10 carbon atoms, aralkyl of 7–15 carbon atoms, halogen, trifluoromethyl, alkoxy of 1–6 carbon atoms, Het–alkyl wherein the alkyl moiety contains 1–6 carbon atoms, or aryl of 6–10 carbon atoms mono–, di–, or tri–substituted with trifluoromethyl, alkyl of 1–6 carbon atoms or, alkoxy of 1–6 carbon atoms; Het is (e) or (f); R^7 is alkylene of 1 to 3 carbon atoms, G is oxygen, sulfur or nitrogen; R^2 is hydrogen, alkyl of 1–6 carbon atoms, alkoxy of 1–6 carbon atoms, halogen, or trifluoromethyl; R^3 and R^4 are each, independently, hydrogen, halogen, alkyl of 1–6 carbon atoms, aryl of 6–10 carbon atoms, halogen, trifluoromethyl, alkoxy of 1–6 carbon atoms, aryl of 6–10 carbon atoms mono–, di–, or tri–substituted with trifluoromethyl, alkyl of 1–6 carbon atoms or, alkoxy of 1–6 carbon atoms, nitro, alkylsulfamide; arylsulfamide, cycloakyl of 3–8 carbon atoms or a heterocyclic ring containing 5 to ring 7 atom rings having 1 to 3 heteroatoms selected from oxygen, nitrogen, or sulfur; R^5 is hydrogen, alkyl of 1–6 carbon atoms, aryl of 6–10 carbon atoms, or aralkyl of 7–15 carbon atoms; R^6 is hydrogen, $-OR^5$, or $-OCOR^5$; with the proviso that when R^1 is halogen, Y is a bond, or a pharmaceutically acceptable salt thereof, which are useful in treating metabolic disorders related to insulin resistance or hyperglycemia.

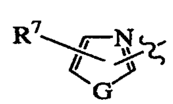

(I)

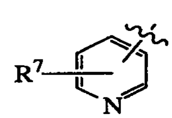

(a)


(b)


(c)


(d)


(e)


(f)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania
AM	Armenia
AT	Austria
AU	Australia
AZ	Azerbaijan
BA	Bosnia and Herzegovina
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CU	Cuba
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GH	Ghana
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IL	Israel
IS	Iceland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgyzstan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakstan
LC	Saint Lucia
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LS	Lesotho
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
MK	The former Yugoslav Republic of Macedonia
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

BIPHENYL SULFONYL ARYL CARBOXYLIC ACIDS USEFUL IN THE TREATMENT OF INSULIN RESISTANCE AND HYPERGLYCEMIA

BACKGROUND OF THE INVENTION

The prevalence of insulin resistance in glucose intolerant subjects has long been recognized. Reaven et al (*American Journal of Medicine* 1976, *60*, 80) used a continuous infusion of glucose and insulin (insulin/glucose clamp technique) and oral glucose tolerance tests to demonstrate that insulin resistance existed in a diverse group of nonobese, nonketotic subjects. These subjects ranged from borderline glucose tolerant to overt, fasting hyperglycemia. The diabetic groups in these studies included both insulin dependent (IDDM) and noninsulin dependent (NIDDM) subjects.

Coincident with sustained insulin resistance is the more easily determined hyperinsulinemia, which can be measured by accurate determination of circulating plasma insulin concentration in the plasma of subjects. Hyperinsulinemia can be present as a result of insulin resistance, such as is in obese and/or diabetic (NIDDM) subjects and/or glucose intolerant subjects, or in IDDM subjects, as a consequence of over injection of insulin compared with normal physiological release of the hormone by the endocrine pancreas.

The association of hyperinsulinemia with obesity and with ischemic diseases of the large blood vessels (e.g. atherosclerosis) has been well established by numerous experimental, clinical and epidemiological studies (summarized by Stout, *Metabolism* 1985, *34*, 7, and in more detail by Pyorala et al, *Diabetes/Metabolism Reviews* 1987, *3*, 463). Statistically significant plasma insulin elevations at 1 and 2 hours after oral glucose load correlates with an increased risk of coronary heart disease.

Since most of these studies actually excluded diabetic subjects, data relating the risk of atherosclerotic diseases to the diabetic condition are not as numerous, but point in the same direction as for nondiabetic subjects (Pyorala et al). However, the incidence of atherosclerotic diseases in morbidity and mortality statistics in the diabetic population exceeds that of the nondiabetic population (Pyorala et al; Jarrett *Diabetes/Metabolism Reviews* 1989,*5*, 547; Harris et al, Mortality from diabetes, in *Diabetes in America 1985*).

The independent risk factors obesity and hypertension for atherosclerotic diseases are also associated with insulin resistance. Using a combination of insulin/glucose clamps, tracer glucose infusion and indirect calorimetry, it has been

demonstrated that the insulin resistance of essential hypertension is located in peripheral tissues (principally muscle) and correlates directly with the severity of hypertension (DeFronzo and Ferrannini, *Diabetes Care* 1991, *14,* 173). In hypertension of the obese, insulin resistance generates hyperinsulinemia, which is recruited as a mechanism to limit further weight gain via thermogenesis, but insulin also increases renal sodium reabsorption and stimulates the sympathetic nervous system in kidneys, heart, and vasculature, creating hypertension.

It is now appreciated that insulin resistance is usually the result of a defect in the insulin receptor signaling system, at a site post binding of insulin to the receptor. Accumulated scientific evidence demonstrating insulin resistance in the major tissues which respond to insulin (muscle, liver, adipose), strongly suggests that a defect in insulin signal transduction resides at an early step in this cascade, specifically at the insulin receptor kinase activity, which appears to be diminished (reviewed by Haring, *Diabetalogia* 1991, *34*, 848).

Protein-tyrosine phosphatases (PTPases) play an important role in the regulation of phosphorylation of proteins. The interaction of insulin with its receptor leads to phosphorylation of certain tyrosine molecules within the receptor protein, thus activating the receptor kinase. PTPases dephosphorylate the activated insulin receptor, attenuating the tyrosine kinase activity. PTPases can also modulate post-receptor signaling by catalyzing the dephosphorylation of cellular substrates of the insulin receptor kinase. The enzymes that appear most likely to closely associate with the insulin receptor and therefore, most likely to regulate the insulin receptor kinase activity, include PTP1B, LAR, PTPα and SH-PTP2 (B. J. Goldstein, *J. Cellular Biochemistry* 1992, *48*, 33; B. J. Goldstein, *Receptor* 1993, *3*, 1-15,; F. Ahmad and B. J. Goldstein *Biochim. Biophys Acta* 1995, *1248*, 57-69).

McGuire et al. (*Diabetes* 1991, *40*, 939), demonstrated that nondiabetic glucose intolerant subjects possessed significantly elevated levels of PTPase activity in muscle tissue vs. normal subjects, and that insulin infusion failed to suppress PTPase activity as it did in insulin sensitive subjects.

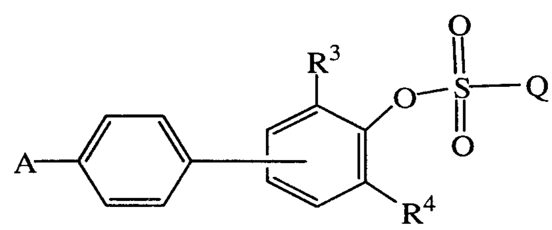
Meyerovitch et al (*J. Clinical Invest.* 1989, *84*, 976) observed significantly increased PTPase activity in the livers of two rodent models of IDDM, the genetically diabetic BB rat, and the STZ-induced diabetic rat. Sredy et al (*Metabolism,* 44, 1074, 1995) observed similar increased PTPase activity in the livers of obese, diabetic ob/ob mice, a genetic rodent model of NIDDM.

The compounds of this invention have been shown to inhibit PTPases derived from rat liver microsomes and human-derived recombinant PTPase-1B (hPTP-1B) *in*

vitro. They are useful in the treatment of insulin resistance associated with obesity, glucose intolerance, diabetes mellitus, hypertension and ischemic diseases of the large and small blood vessels.

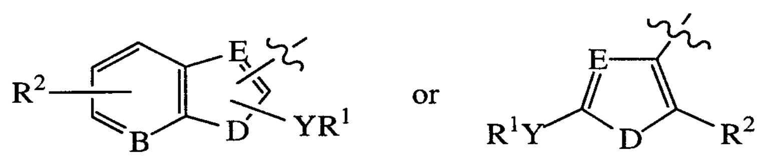
DESCRIPTION OF THE INVENTION

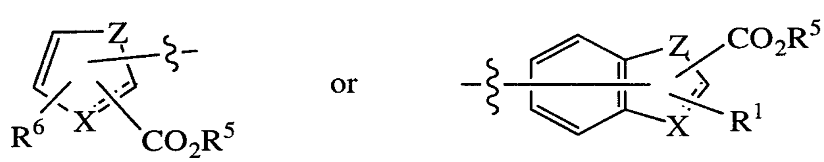
This invention provides a compound of formula I having the structure



I

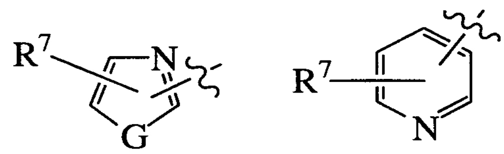
wherein

A is  ;

Q is  ;

B is carbon or nitrogen;
D is oxygen, sulfur, or nitrogen;
E is carbon or nitrogen;
X is carbon, nitrogen, oxygen, or sulfur;
Y is a bond, methylene, C(O), or CH(OH);
Z is CH=CH, nitrogen, oxygen, or sulfur;
the dashed line of Q represents an optional double bond;

R^1 is alkyl of 1 to 12 carbons, aryl of 6-10 carbon atoms, aralkyl of 7-15 carbon atoms, halogen, trifluoromethyl, alkoxy of 1-6 carbon atoms, Het-alkyl wherein the alkyl moiety contains 1-6 carbon atoms, or aryl of 6-10 carbon atoms mono-, di- or tri-substituted with trifluoromethyl, alkyl of 1-6 carbon atoms or, alkoxy of 1-6 carbon atoms;

Het is  ;

R^7 is alkylene of 1 to 3 carbon atoms;

G is oxygen, sulfur or nitrogen;

R^2 is hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, or trifluoromethyl;

R^3 and R^4 are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, aryl of 6-10 carbon atoms, halogen, trifluoromethyl, alkoxy of 1-6 carbon atoms, aryl of 6-10 carbon atoms mono-, di-, or tri-substituted with trifluoromethyl, alkyl of 1-6 carbon atoms or, alkoxy of 1-6 carbon atoms, nitro, alkylsulfamide; arylsulfamide, cycloalkyl of 3-8 carbon atoms or a heterocyclic ring containing 5 to ring 7 atom rings having 1 to 3 heteroatoms selected from oxygen, nitrogen, or sulfur;

R^5 is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6-10 carbon atoms mono-, di-, or tri-substituted with trifluoromethyl, halogen, alkyl of 1-6 carbon atoms, aralkyl of 7-15 carbon atoms, or heteroaryl ;

R^6 is hydrogen, $-OR^5$, or $-OCOR^5$;

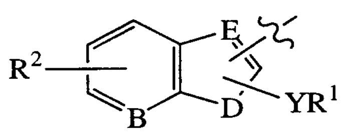
with the proviso that when R^1 is halogen, Y is a bond;

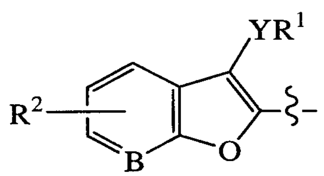
or a pharmaceutically acceptable salt thereof, which are useful in treating metabolic disorders related to insulin resistance or hyperglycemia.

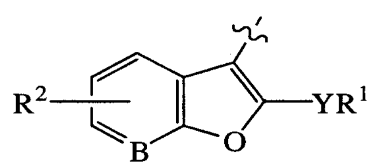
Pharmaceutically acceptable salts can be formed from organic and inorganic acids, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, napthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable acids when a compound of this invention contains a basic moiety. Salts may also be formed from organic and inorganic bases, preferably alkali metal salts, for example, sodium, lithium, or potassium, when a compound of this invention contains a carboxylate or phenolic moiety, or similar moiety capable of forming base addition salts.

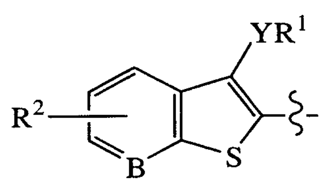
Alkyl includes both straight chain as well as branched moieties. Halogen means bromine, chlorine, fluorine, and iodine. It is preferred that the aryl portion of the aryl or aralkyl substituent is a phenyl, naphthyl or 1,4-benzodioxan-5-yl group; with phenyl being most preferred. The aryl moiety may be optionally mono-, di-, or tri- substituted with a substituent selected from the group consisting of alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, trifluoromethyl, halogen, alkoxycarbonyl of 2-7 carbon atoms, alkylamino of 1-6 carbon atoms, and dialkylamino in which each of the alkyl groups is of 1-6 carbon atoms, nitro, cyano, $-CO_2H$, alkylcarbonyloxy of 2-7 carbon atoms, and alkylcarbonyl of 2-7 carbon atoms.

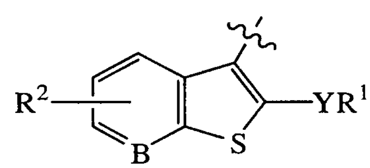
The compounds of this invention may contain an asymmetric carbon atom and some of the compounds of this invention may contain one or more asymmetric centers and may thus give rise to optical isomers and diastereomers. While shown without respect to stereochemistry in Formula I, the present invention includes such optical isomers and diastereomers; as well as the racemic and resolved, enantiomerically pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof.

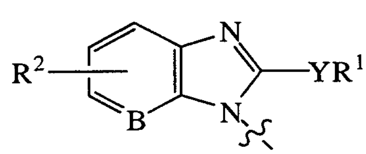
When A is  , the following compounds of A are preferred:

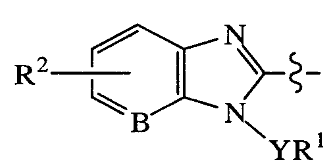


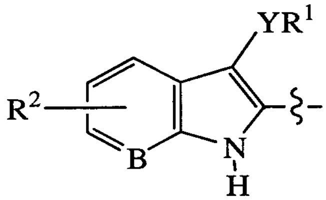


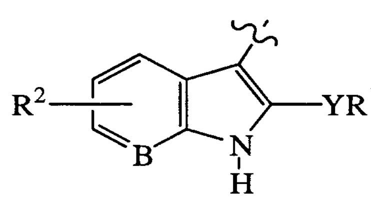


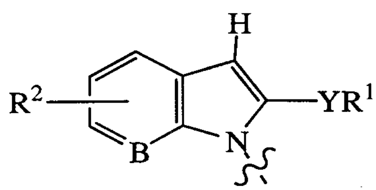


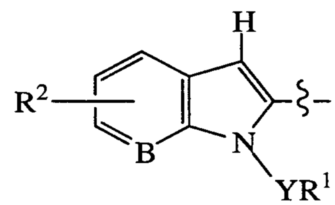


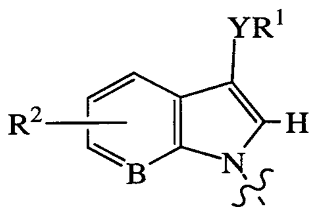


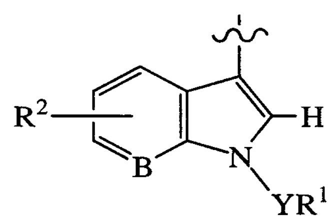


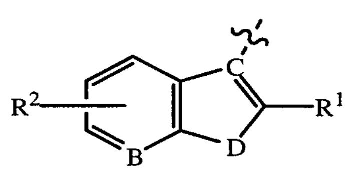






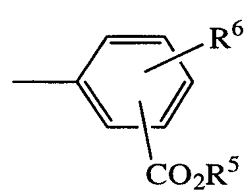




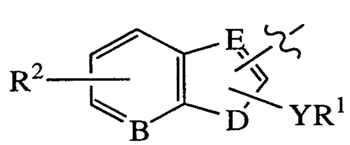
It is more preferred that A is 

and D is O or S.

Similarly, allowed compounds (based on correct number of bonds) of Q can readily be recognized by one skilled in the art. It is more preferred that Q is:



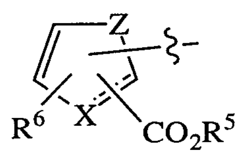
Preferred compounds of this invention are those compounds of Formula I, wherein:

A is  ;

B is -CH-;

E is -CH-;

D is oxygen or suflur;

Q is  ;

Z is CH=CH;

X is carbon;

or a pharmaceutically acceptable salt thereof.

Specifically preferred compounds of the present invention are set forth below:

4-[4'-(2-benzyl-benzofuran-3-yl)-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

5-[4'-(2-benzyl-benzofuran-3-yl)-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

4-[4'-(2-benzyl-benzofuran-3-yl)-biphenyl-4-yloxysulfonyl]-benzoic acid

3-[4'-(2-benzyl-benzofuran-3-yl)-biphenyl-4-yloxysulfonyl]-benzoic acid

4-[4'-(2-benzyl-benzo[b]thiopen-3-yl)-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

4-[4'-(2-benzyl-benzo[b]thiopen-3-yl)-3-bromo-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

4-[4'-(2-benzyl-benzo[b]thiopen-3-yl)-3,5-dibromo-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

4-[4'-(2-benzyl-benzofuran -3-yl)-3,5-dimethyl-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

4-[4'-(2-benzoyl-benzofuran-3-yl)-3-nitro-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

4-[4'-(2-benzyl-benzofuran-3-yl)-3-bromo-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

4-[4'-(2-benzoyl-benzofuran-3-yl)-3-cyclopentyl-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

4-[4'-(2-benzyl-4,5-dimethyl-thiopen-3-yl)-3-bromo-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

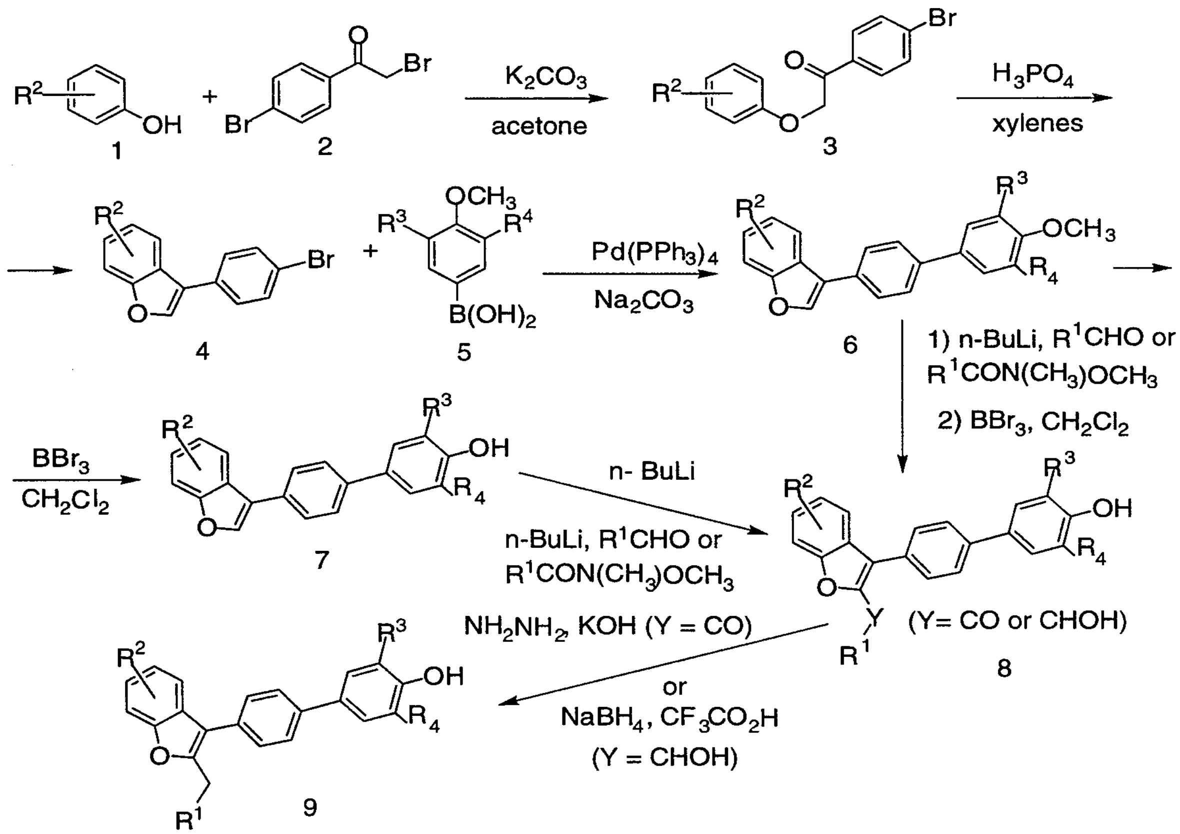
4-(4'-benzofuran-3-yl)-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

2-hydroxy-4-{3'-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-yl]-biphenyl-4-yloxysulfonyl}-benzoic acid

or a pharmaceutically acceptable salt thereof.

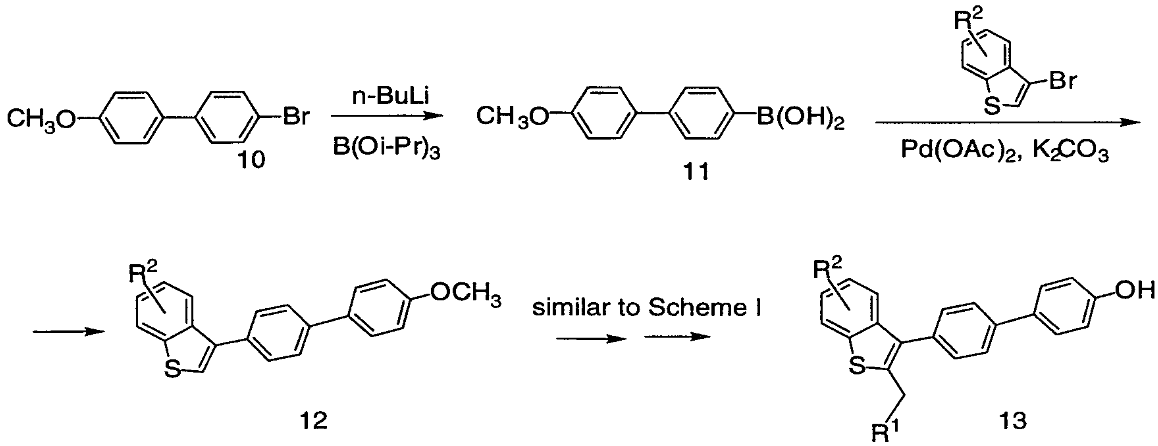
The compounds of this invention were be prepared according to the following schemes from commercially available starting materials or starting materials which can be prepared using to literature procedures. These schemes show the preparation of representative compounds of this invention.

Scheme I



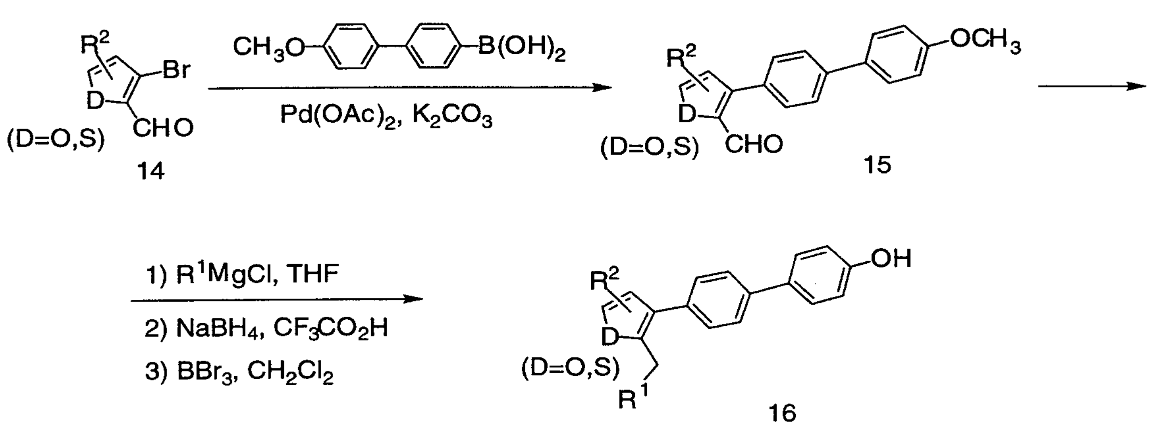
In Scheme I, commercially available phenols (1; R^2 as defined above) were treated with 4-bromophenacyl bromide (2) in the presence of potassium carbonate to produce ketones (3). Compounds (3) were treated with polyphosphoric acid at high temperatures (150 C°) to afford benzofurans (4) [ref. J. Med. Chem. 1989, 32, 1700-1707]. Benzofurans (4) were coupled with aryl boronic acids of general structure (5; R^3, R^4 are alkyl, aryl, trifluoromethyl, substituted aryl, nitro, carbocyclic 5 to 7 carbon atoms rings or heterocyclic rings 5 to 7 atom rings with from 1 to 3 heteroatoms selected from oxygen, nitrogen, and sulfur) using the Suzuki protocol [ref. Syn. Comm. 1981, 11, 513-519] to produce biphenyls (6). The aryl boronic acids are either commercially available or can be prepared according to known methodology [ref. J. Org. Chem, 1984, 49, 5237-5243]. Biphenyls (6) were converted to biphenyls (8) using two different synthetic approaches. In the first synthetic approach, biphenyls (6) were treated first with n-BuLi and either aldehydes R^1CHO or "Weinreb" amides $R^1CON(CH_3)OCH_3$ (R^1 is as defined above with the exception of halogen), and secondly with boron tribromide in dichloromethane to produce biphenyls (8). In the second synthetic approach, biphneyls (6) first converted to biphenyls (7) with boron tribromide in dichloromethane [ref. J. Org. Chem. 1974, 39, 1427-1429], and then (7) were converted to biphenyls (8) by using n-BuLi and either aldehydes R^1CHO or "Weinreb" amides $R^1CON(CH_3)OCH_3$. The required aldehydes and "Weinreb" amides are either commercially available or can be prepared according to known synthetic methodology [ref. Tet. Lett. 1993, 34, 6215-6218]. Biphenyls (8) were converted to biphenyls (9) by reduction of the ketones (Y = CO) using the Wolff-Kishner reduction (NH_2NH_2, KOH; ref. Org. Reactions, 1948, 4, 378), or reduction of the secondary hydroxy group (Y = CHOH) with sodium borohydride in trifluoroacetic acid [ref. Syn. Comm. 1990, 20, 487-493].

Scheme II



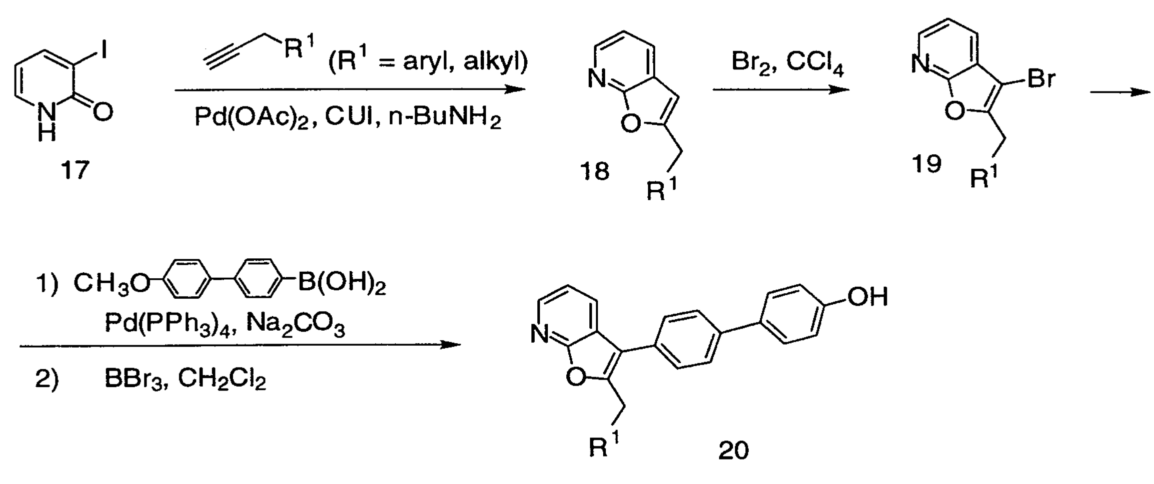
In Scheme II, the biphenyl boronic acid (11) was prepared from 10 according to known methodology [ref. J. Org. Chem. 1984, 49, 5237-5243] using n-BuLi to generate the aryllithium intermediate which was subsequently treated with triisopropyl borate. Boronic acid (11) was coupled with 3 -bromobenzothiophenes (prepared according to reference J. Am. Chem. Soc. 1950, 72, 571-574) using the Suzuki protocol [ref. Syn. Comm. 1981, 11, 513-519] to produce biphenyls (12). Biphenyls (12) were converted to the biphenyls (13) in a similar manner as described in Scheme I for the conversion of biphenyls (6) to biphenyls (9).

Scheme III



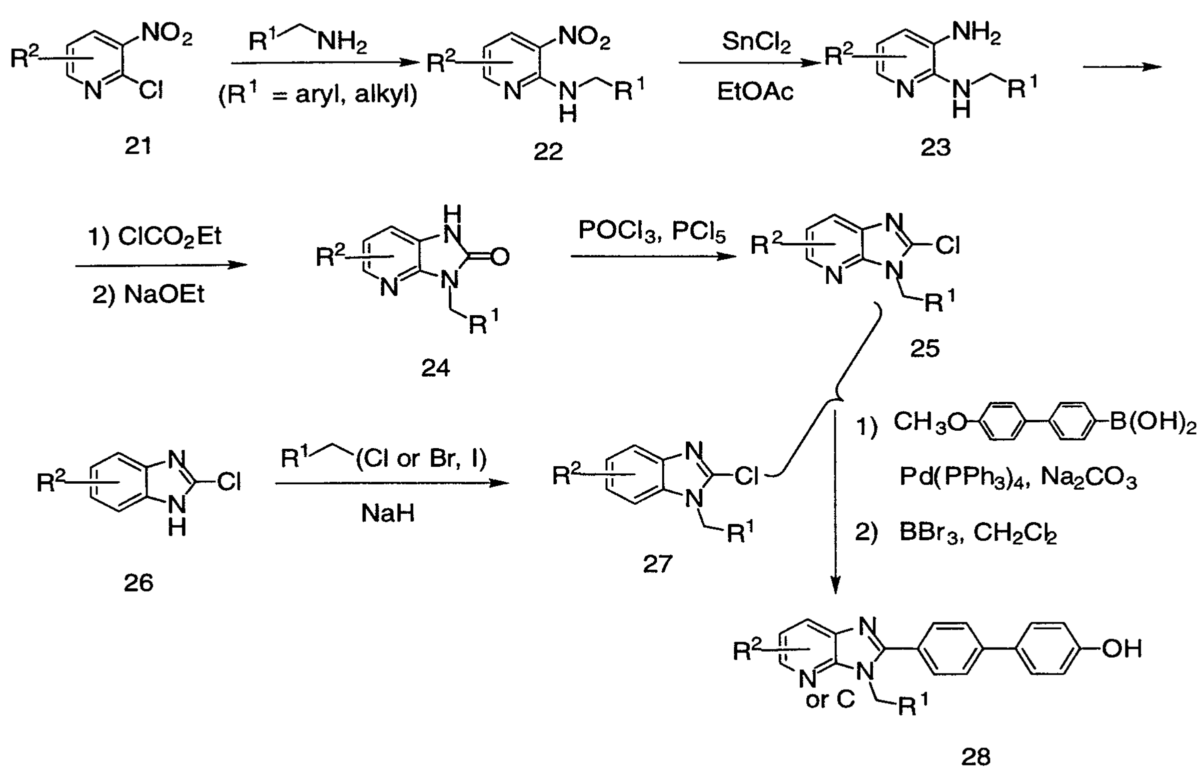
In Scheme III, thienyl and furyl aldehydes (14) are either commercially available or can be prepared from substituted furans or thiophenes. Furans or thiophenes undergo metallation at the 2-position with alkyllithium reagents [J. Chem. Soc. Perkin I, 1977, 887] which upon treatment first with a formylating agent (i.e., dimethylformamide), and secondly bromination according to known methodology [ref. J. Am. Chem. Soc. 1950, 72, 571-574] to afford the required compounds (14). Coupling of aldehydes (14) with 4, 4'-methoxy biphenyl boronic acid using the Suzuki protocol [ref. Syn. Comm. 1981, 11, 513-519] gave biphenyls (15). Known or easily prepared Grignard Reagents [ref. Chem. Re. 1954, 54, 835] $R^1Mg(Cl$ or $Br)$ (R^1 is as defined above with the exception of halogen, trifluoromethyl, lower alkoxy) were first treated with aldehydes (14), followed by reduction of the produced methyl-hydroxy compounds with sodium borohydride and trifluoroacetic acid, and then demethylation with boron tribromide in dichoromethane to afford biphenyls (16).

Scheme IV



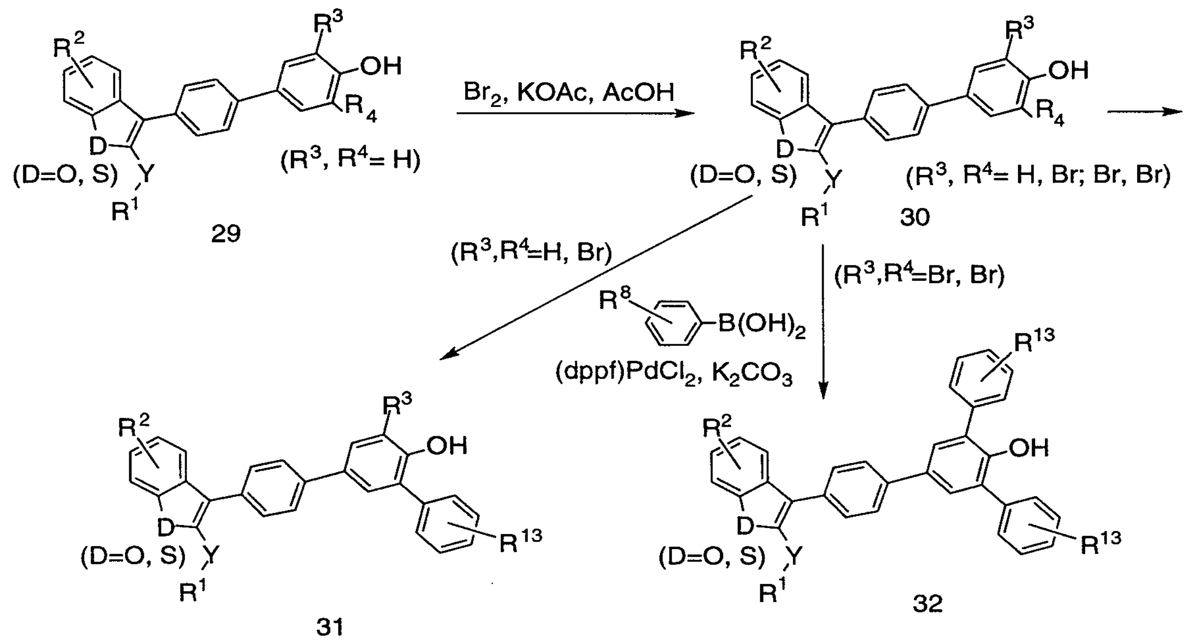
In Scheme IV, the furo[2,3-b]pyridines (18) (R^1 is aryl or alkyl) were prepared according to known methodology [ref. Tet. Lett. 1994, 35, 9355-9358]. Bromination of 18 with Br_2, in carbon tetrachloride produced 19. Pyridines (19) were converted to biphenyls (20) in a similar manner as described in Scheme I by Suzuki coupling with 4, 4'-methoxy biphenyl boronic acid, and demethylation with boron tribromide.

Scheme V



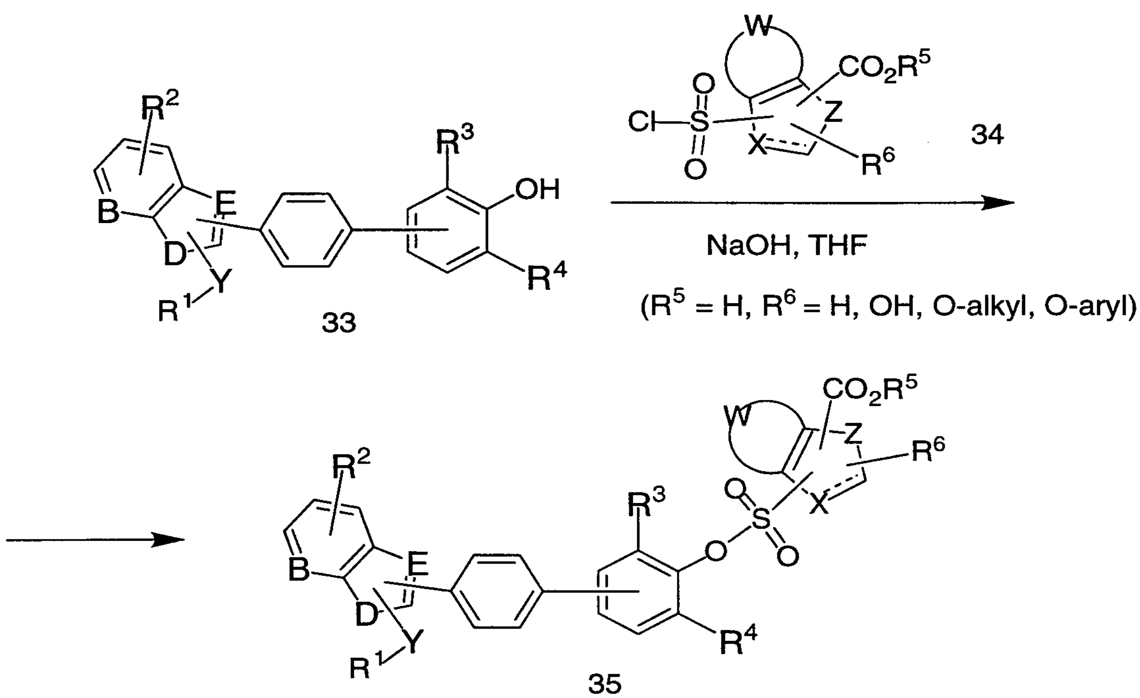
In Scheme V, the chloro-nitro-pyridines (21) were treated with primary amines to produce nitro-pyridines (22). The nitro-pyridines (22) were reduced with tin chloride to anilines (23), which upon treatment with ethyl chloroformate and sodium ethoxide gave imidazolones (24). The imidazolones (24) were converted to the 2-chloro-imidazole[4,5-b]pyridines (25). 2-Chlorobenzimidazoles (26) were alkylated in the presence of sodium hydride to give benzimidazoles (27). Both, the imidazole[4,5-b]pyridines (25), and benzimidazoles (27) were converted to the biphenyls (28) in a similar manner as described in Scheme I by Suzuki coupling with 4, 4'-methoxy biphenyl boronic acid, and demethylation with boron tribromide.

Scheme VI



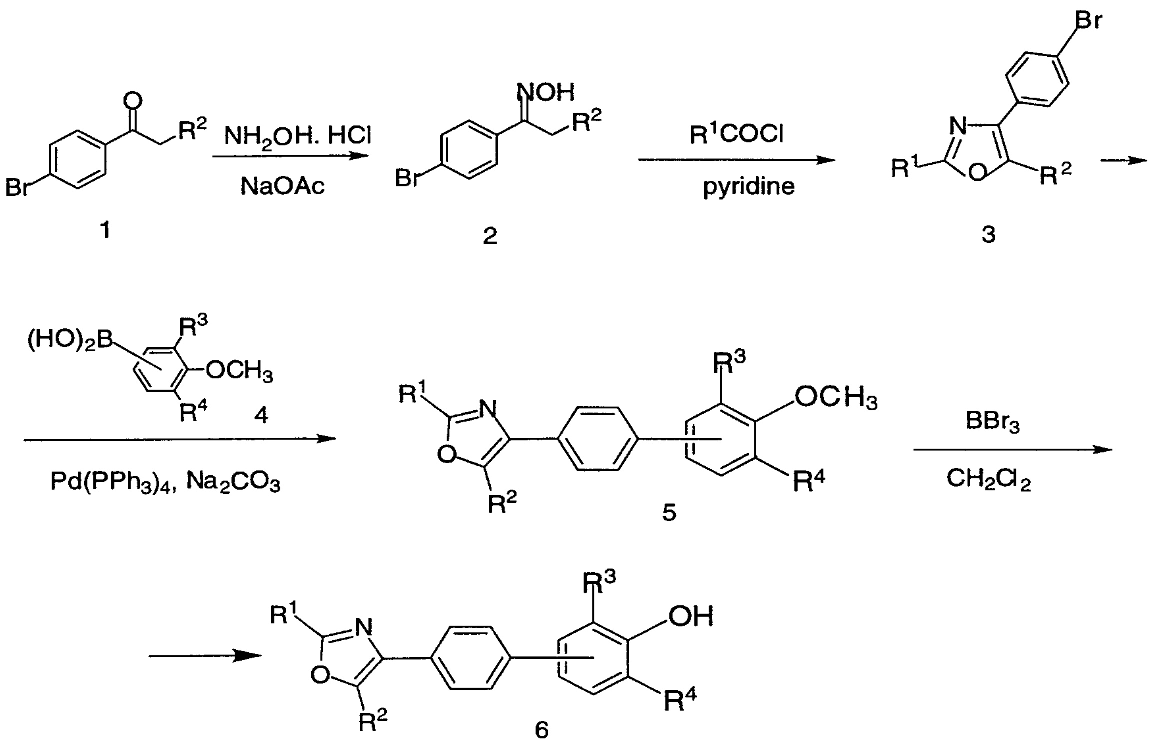
In Scheme VI, the biphenyl compounds (29; Y = CO, CH_2) can be monobrominated or dibrominated using bromine, potassium acetate and acetic acid. One equivalent of bromine in a high dilution reaction mixture and low temperatures in the range of 5-10 C° afforded predominantly the monobrominated product (30; R^3, R^4 = H, Br). The dibrominated product (30; R^3, R^4 = Br, Br) was obtained with two equivalents of bromine at room temperature. The Suzuki coupling protocol [ref. Syn. Comm. 1981, 11, 513-519] was used to generate the terphenyls 31 and 32. Coupling of the monobromo compounds (30; R^3, R^4 = H, Br) with boronic acids R^8-Ar-$B(OH)_2$; (R^8 = halogen, trifluoromethyl, alkoxy, alkyl, nitro, amino, carboalkoxy) in the present of an inorganic base, for example K_2CO_3, $Ba(OH)_2$, and palladium (0 or II) catalyst, for example $Pd(PPh_3)_4$, $Pd(OAc)_2$, $(dppf)PdCl_2$, produced terphenyls (31; R^3 = H). Similarly, the dibromo compounds (30; R^3, R^4 = Br, Br) can undergo Suzuki coupling to afford either the di-coupled product (32) by using 2 equivalents of boronic acid at high temperatures (100 °C), or the mono-coupled-mono-bromo product (31; R^3, R^4 = Br, Aryl-R^{13}). Both the bromo and dibromo compounds can afford in the same synthetic manner products with various heterocyclic boronic acids, for example thiophene, furan, oxazole, thiazole, pyridine).

Scheme VII



In Scheme VII phenols (33) were treated with sulfonyl chlorides (34) in the presence of an inorganic base, for example sodium hydroxide in a polar solvent, for example tetrahydrofuran. The sulfonyl chlorides are commercially available or can be obtained by known sulfonylation protocols, for example treatment of an aromatic or heteroaromatic substrate with chlorosulfonic acid. The W-ring represents an optionally fused phenyl ring, which can be present or absent as defined by Q. The esters of the obtained carboxylic acids can be obtained by the known Fisher esterification protocol.

Scheme VIII



In Scheme VIII commercially available ketones (1) were treated with hydroxylamine in the presence of sodium acetate to produce oximes (2). Oximes (2) were converted to oxazoles by a known methodology [ref. Tet. Lett. 1980, 21, 2359-2360), where oximes (2) were treated with acetyl chlorides in the presence of pyridine to produce oxazoles (3). Oxazoles (3) were coupled with aryl boronic acids of general structure (4; R^3, R^4 are alkyl, aryl, trifluoromethyl, substituted aryl, nitro, carbocyclic 5 to 7 carbon atoms rings or heterocyclic rings 5 to 7 atom rings with from 1 to 3 heteroatoms selected from oxygen, nitrogen, and sulfur) using the Suzuki protocol [ref. Syn. Comm. 1981, 11, 513-519] to produce biphenyls (5). The aryl boronic acids are either commercially available or can be prepared according to known methodology [ref. J. Org. Chem, 1984, 49, 5237-5243]. Biphenyls (5) were converted to phenols (6) by treatment with boron tribromide in dichloromethane [ref. J. Org. Chem. 1974, 39, 1427-1429].

The compounds of this invention are useful in treating metabolic disorders related to insulin resistance or hyperglycemia, typically associated with obesity or

glucose intolerance. The compounds of this invention are therefore, particularly useful in the treatment or inhibition of type II diabetes. The compounds of this invention are also useful in modulating glucose levels in disorders such as type I diabetes.

The ability of compounds of this invention to treat or inhibit disorders related to insulin resistance or hyperglycemia was established with representative compounds of this invention in the following standard pharmacological test procedure which measures the inhibition of PTPase, and an in vivo standard pharmacological test procedure which measures the blood glucose lowering activity of representative compounds of this invention.

Inhibition of Tri-Phosphorylated Insulin Receptor Dodecaphosphopeptide Dephosphorylation by hPTP1B

This standard pharmacological test procedure assess the inhibition of recombinant rat protein tyrosine phosphatase, PTP1B, activity using, as substrate, the phosphotyrosyl dodecapeptide corresponding to the 1142-1153 insulin receptor kinase domain, phosphorylated on the 1146, 1150 and 1151 tyrosine residues. The procedure used and results obtained are briefly described below.

Human recombinant PTP1B was prepared as described by Goldstein (see Goldstein et al. *Mol. Cell. Biochem.* **109**, 107, **1992**). The enzyme preparation used was in microtubes containing 500-700 μg/ml protein in 33 mM Tris-HCl, 2 mM EDTA, 10% glycerol and 10 mM 2-mercaptoethanol.

Measurement of PTPase activity. The malachite green-ammonium molybdate method, as described (Lanzetta **et al.** ***Anal. Biochem.*** **100**, 95, **1979**) and adapted for a platereader, is used for the nanomolar detection of liberated phosphate by recombinant PTP1B. The test procedure uses, as substrate, a dodecaphosphopeptide custom synthesized by AnaSpec, Inc. (San Jose, CA). the peptide, TRDIYETDYYRK, corresponding to the 1142-1153 catalytic domain of the insulin receptor, is tyrosine phosphorylated on the 1146, 1150, and 1151 tyrosine residues. The recombinant rPTP1B is diluted with buffer (pH 7.4, containing 33 mM Tris-HCl, 2 mM EDTA and 50 mM b-mercaptoethanol) to obtain an approximate activity of 1000-2000 nmoles/min/mg protein. The diluted enzyme (83.25 mL) is preincubated for 10 min at 37^{O}C with or without test compound (6.25 mL) and 305.5 mL of the 81.83 mM

HEPES reaction buffer, pH 7.4 peptide substrate, 10.5 ml at a final concentration of 50 mM, and is equilibrated to 37°C. in a LABLINE Multi-Blok heater equipped with a titerplate adapter. The preincubated recombinant enzyme preparation (39.5 ml) with or without drug is added to initiate the dephosphorylation reaction, which proceeds at 37°C for 30 min. The reaction is terminated by the addition of 200 mL of the malachite green-ammonium molybdate-Tween 20 stopping reagent (MG/AM/Tw). The stopping reagent consists of 3 parts 0.45% malachite green hydrochloride, 1 part 4.2% ammonium molybdate tetrahydrate in 4 N HCl and 0.5% Tween 20. Sample blanks are prepared by the addition of 200 mL MG/AM/Tw to substrate and followed by 39.5 ml of the preincubated recombinant enzyme with or without drug. The color is allowed to develop at room temperature for 30 min. and the sample absorbances are determined at 650 nm using a platereader (Molecular Devices). Sample and blanks are prepared in quadruplicates.

Calculations: PTPase activities, based on a potassium phosphate standard curve, are expressed as nmoles of phosphate released/min/mg protein. Inhibition of recombinant PTP1B by test compounds is calculated as percent of phosphatase control. A four parameter non-linear logistic regression of PTPase activities using SAS release 6.08, PROC NLIN, is used for determining IC_{50} values of test compounds. The following results were obtained.

Example	IC50 (µM)
1	0.039
2	0.026
3	0.075
4	0.106
5	0.354
6	0.034
7	0.029
8	0.178
9	0.040
10	0.032
11	0.028
12	0.024

Example	IC50 (μM)
13	0.030
14	0.193
Phenylarsine oxide (reference standard)	39.7
Sodium orthovanadate (reference standard)	244.8
Ammonium molybdate tetrahydrate (reference standard)	8.7

The blood glucose lowering activity of representative compounds of this invention were demonstrated in an in vivo standard procedure using diabetic (ob/ob) mice. The procedures used and results obtained are briefly described below.

The non-insulin dependent diabetic (NIDDM) syndrome can be typically characterizes by obesity, hyperglycemia, abnormal insulin secretion, hyperinsulinemia and insulin resistance. The genetically obese-hyperglycemic ob/ob mouse exhibits many of these metabolic abnormalities and is thought to be a useful model to search for hypoglycemic agents to treat NIDDM [Coleman, D.: Diabetologia **14**: 141-148, 1978].

In each test procedure, mice [Male or female ob/ob (C57 Bl/6J) and their lean litermates (ob/+ or +/+, Jackson Laboratories) ages 2 to 5 months (10 to 65 g)] of a similar age were randomized according to body weight into 4 groups of 10 mice. The mice were housed 5 per cage and are maintained on normal rodent chow with water ad libitum. Mice received test compound daily by gavage (suspended in 0.5 ml of 0.5% methyl cellulose); dissolved in the drinking water; or admixed in the diet. The dose of compounds given ranges from 2.5 to 200 mg/kg body weight/day. The dose is calculated based on the fed weekly body weight and is expressed as active moiety. The positive control, ciglitazone (5-(4-(1-methylcyclohexylmethoxy)benzyl)-2,4-dione, see Chang, A., Wyse, B., Gilchrist, B., Peterson, T. and Diani, A. Diabetes **32**: 830-838, 1983.) was given at a dose of 100 mg/kg/day, which produces a significant lowering in plasma glucose. Control mice received vehicle only.

On the morning of Day 4, 7 or 14 two drops of blood (approximetly 50 ul) were collected into sodium fluoride containing tubes either from the tail vein or after decapitation. For those studies in which the compound was administered daily by gavage the blood samples were collected two hours after compound administration. The plasma was isolated by centrifugation and the concentration of glucose is measured enzymatically on an Abbott V.P. Analyzer.

For each mouse, the percentage change in plasma glucose on Day 4, 7 or 14 is calculated relative to the mean plasma glucose of the vehicle treated mice. Analysis of variance followed by Dunett's Comparison Test (one-tailed) are used to estimate the significant difference between the plasma glucose values from the control group and the individual compound treated groups (CMS SAS Release 5.18).

The results shown in the table below shows that the compounds of this invention are antihyperglycemic agents as they lower blood glucose levels in diabetic mice.

Example	Dose (mg/Kg)	% Change Glucose from Vehicle
13	25	-24.6[a]
Ciglitazone (reference standard	100	-43

a Statistically ($p < 0.05$) significant.

Based on the results obtained in the standard pharmacological test procedures, representative compounds of this invention have been shown to inhibit PTPase activity and lower blood glucose levels in diabetic mice, and are therefore useful in treating metabolic disorders related to insulin resistance or hyperglycemia, typically associated with obesity or glucose intolerance. More particularly, the compounds of this invention useful in the treatment or inhibition of type II diabetes, and in modulating glucose levels in disorders such as type I diabetes. As used herein, the term modulating means maintaining glucose levels within clinically normal ranges.

Effective administration of these compounds may be given at a daily dosage of from about 1 mg/kg to about 250 mg/kg, and may given in a single dose or in two or more divided doses. Such doses may be administered in any manner useful in directing the active compounds herein to the recipient's bloodstream, including orally, via implants, parenterally (including intravenous, intraperitoneal and subcutaneous injections), rectally, vaginally, and transdermally. For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present

compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

It is understood that the dosage, regimen and mode of administration of these compounds will vary according to the malady and the individual being treated and will be subject to the judgment of the medical practitioner involved. It is preferred that the administration of one or more of the compounds herein begin at a low dose and be increased until the desired effects are achieved.

The following procedures describe the preparation of representative examples of this invention.

Example 1

4-[4'-(2-Benzyl-benzofuran-3-yl)-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

Step a) ω-Phenoxy-4-bromoacetophenone

Potassium carbonate (24.8 g, 179.8 mmol) was added into a mixture of 2,4'-dibromoacetophenone (50.0 g, 179.8 mmol), phenol (16.9 g, 179.8mmol) and dry acetone (200mL). The reaction mixture was refluxed for 12 hours, cooled to room temperature, poured into water, and extracted with ethyl ether. The organic extracts were dried over $MgSO_4$. Evaporation gave a yellow solid (49.6 g, 94% yield): MS *m/e* 291 (M^+).

Step b) 3-(4-Bromophenyl)-1-benzofuran

A mixture of ω-phenoxy-4-bromoacetophenone (49.0 g, 167.8 mmol), polyphosphoric acid (100 g) and xylenes (300 mL) was refluxed for 12 hours. The reaction mixture cooled to room temperature, poured into water, and extracted with ethyl ether. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography on silica gel (hexanes/EtAOc 40:1) gave a yellow solid (36.2 g, 79% yield): mp 70-71 °C; MS *m/e* 272 (M^+);

Analysis for: $C_{14}H_9BrO$ Calc'd: C, 61.57; H, 3.32; Found: C, 61.80; H, 3.31

Step c) 3-(4'-Methoxy-biphenyl-4-yl)-benzofuran

4-Methoxy-benzeneboronic acid (14.17 g, 70.5 mmol) in ethyl alcohol (10 mL) was added into a mixture of 3-(4-bromophenyl)-1-benzofuran (17.5 g, 64.1mmol), sodium carbonate (2N, 64.1 mL), tetrakis(triphenylphosphine)palladium(0) (2.23 g, 1.92 mmol), and toluene (200 mL). The reaction mixture was refluxed for 12 hours, cooled to room temperature, and treated with hydrogen peroxide (30%, 5 mL) for 1 hour. Then, the mixture was poured into water and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation and crystallization from acetone/ethyl ether gave a white solid (14.9 g, 77% yield): mp 137-138 °C; MS *m/e* 300 (M^+);

Analysis for: $C_{21}H_{16}O_2$ Calc'd: C, 83.98; H, 5.37 Found: C, 83.70; H, 5.22

Step d) 4'-Benzofuran-3-yl-biphenyl-4-ol

Boron tribromide (1.0 M, 6.67 mL, 6.67 mmol) was added dropwise into a cold (-78 °C) mixture of 3-(4'-methoxy-biphenyl-4-yl)-benzofuran (2.0 g, 6.67 mmol), and dichloromethane (25 mL). The reaction mixture was allowed to come gradually to

room temperature and stirred for 10 hours. Then the mixture was cooled to 0 °C and methyl alcohol (5 mL) was added dropwise. After stirring for 10 minutes the mixture was poured into water and extracted with ethyl ether. The organic extracts were dried over $MgSO_4$. Evaporation and crystallization from ethyl ether/hexanes gave a yellow solid (1.69 g, 87% yield): mp 174-175; MS *m/e* 286 (M^+);

Analysis for: $C_{20}H_{14}O_2$ Calc'd: C, 83.90; H, 4.93 Found: C, 83.69; H, 4.88

Step e) <u>[3-(4'-Hydroxy-biphenyl-4-yl)-benzofuran-2-yl]-phenyl-methanone</u>

n-Butyllithium (2.5 N, 8.4 mL, 20.98 mmol) was added dropwise into a cold (-78°C) mixture of 4'-benzofuran-3-yl-biphenyl-4-ol (3.0 g, 10.49 mmol) and tetrahydrofuran (50 mL). The mixture was allowed to gradually warm up to -40°C and stirred for 3 hours. N-Methoxy N-methyl benzamide (1.6 mL, 10.49 mmol) was added dropwise into the mixture. The reaction mixture was allowed to gradually warm up to 0 °C and stirred for 30 minutes. The reaction was quenched with aqueous ammonium chloride, poured into water, acidified with HCl (2N), and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation and crystallization from ethyl ether/hexanes gave a yellow solid (2.9 g, 71% yield): mp 231-232; MS *m/e* 390 (M^+);

Analysis for: $C_{27}H_{18}O_3$ Calc'd: C, 83.06; H, 4.65 Found: C, 82.63; H, 4.27

Step f) <u>4'-(2-Benzyl-benzofuran-3-yl)-biphenyl-4-ol</u>

Hydrazine monohydrate (1.38 g, 27.68 mmol) was added into a mixture of [3-(4'-hydroxy-biphenyl-4-yl)-benzofuran-2-yl]-phenyl-methanone (2.7 g, 6.92 mmol) and diethylene glycol (20 mL). The reaction mixture was stirred at 180 °C for 1 hour. The mixture cooled to room temperature and potassium hydroxide (1.16 g, 20.76 mmol) was gradually added. The mixture stirred at 130 °C for 10 hours, cooled to room temperature, poured into water, and extracted with ethyl ether. The organic extracts were dried over $MgSO_4$. Evaporation and crystallization from ethyl ether/hexanes/acetone gave a white solid (2.45 g, 94% yield): mp 151-153; MS *m/e* 376 (M^+);

Analysis for: $C_{27}H_{20}O_2$ Calc'd: C, 86.15; H, 5.36 Found: C, 85.88; H, 5.13

Step g) <u>4-[4'-(2-Benzyl-benzofuran-3-yl)-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid</u>

Sodium hydroxide (50%) was added dropwise into cold (0 °C) mixture of 4'-(2-benzyl-benzofuran-3-yl)-biphenyl-4-ol (1.0 g, 2.66 mmol), 4-chlorosulfonyl-2-hydroxy-benzoic acid (1.25 g, 5.32 mmol) and tetrahydrofuran (50 mL), in an addition rate that the reaction was maintained at pH 11. The reaction was stirred for 30 minutes, poured into water, acidified with HCl (2 N), and extracted with ethyl ether. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography on acidic silica gel (hexanes/EtAOc 2:1) gave a white solid, (0.67 g, 43% yield): mp 96-98 °C; MS *m/e* 575 $(M-H)^+$;

Analysis for: $C_{34}H_{24}O_7S$ x 0.5 H_2O Calc'd: C, 69.73; H, 4.30 Found: C, 69.83; H, 4.37

Example 2

<u>5-[4'-(2-Benzyl-benzofuran-3-yl)-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid</u>

The title compound was prepared from of 4'-(2-benzyl-benzofuran-3-yl)-biphenyl-4-ol and 5-chlorosulfonyl-2-hydroxy-benzoic acid, in substantially the same manner, as described in Example 1 step g, and was obtained as a white solid, mp 171-173 °C; MS *m/e* 575 $(M-H)^+$;

Analysis for: $C_{34}H_{24}O_7S$ x 0.5 H_20 Calc'd: C, 69.73; H, 4.30 Found: C, 69.86; H, 4.57

Example 3

<u>4-[4'-(2-Benzyl-benzofuran-3-yl)-biphenyl-4-yloxysulfonyl]-benzoic acid</u>

The title compound was prepared from 4'-(2-benzyl-benzofuran-3-yl)-biphenyl-4-ol and 4-chlorosulfonyl-benzoic acid, in substantially the same manner, as described in Example 1 step g, and was obtained as a white solid, mp 186-188 °C; MS *m/e* 559 $(M-H)^+$;

Analysis for: $C_{34}H_{24}O_6S$ x 0.25 H_20 Calc'd: C, 72.26; H, 4.37 Found: C, 72.25; H, 4.17

Example 4

<u>3-[4'-(2-Benzyl-benzofuran-3-yl)-biphenyl-4-yloxysulfonyl]-benzoic acid</u>

The title compound was prepared from of 4'-(2-benzyl-benzofuran-3-yl)-biphenyl-4-ol and 3-chlorosulfonyl-benzoic acid, in substantially the same manner, as

described in Example 1 step g, and was obtained as a white solid, mp 169-171 °C; MS *m/e* 559 $(M-H)^+$;

Analysis for: $C_{34}H_{24}O_6S$ x 0.25 H_20 Calc'd: C, 72.26; H, 4.37 Found: C, 72.20; H, 4.31

Example 5

4-(4'-Benzofuran-3-yl)-biphenyl-4-yloxysulfonyl)-2-hydroxy-benzoic acid

The title compound was prepared from 4'-(benzofuran-3-yl) -biphenyl-4-ol and 4-chlorosulfonyl-2-hydroxy-benzoic acid, in substantially the same manner, as described in Example 1 step g, and was obtained as an off-white solid, mp 218-220 °C; MS *m/e* 485 $(M-H)^+$;

Analysis for: $C_{27}H_{18}O_7S$ Calc'd: C, 66.66; H, 3.73 Found: C, 66.66; H, 3.47

Example 6

4-[4'-(2-Benzyl-benzofuran-3-yl)-3,5-dimethyl-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

The title compound was prepared from 4'-(2-benzyl-benzofuran-3-yl)-3,5-dimethyl-biphenyl-4-ol and 4-chlorosulfonyl-2-hydroxy-benzoic acid, in substantially the same manner, as described in Example 1 step g, and was obtained as a white solid, mp 165-167 °C; MS *m/e* 603 $(M-H)^+$;

Analysis for: $C_{36}H_{28}O_7S$ x 0.5 H_20 Calc'd: C, 70.46; H, 4.76 Found: C, 70.53; H, 4.58

Example 7

4-[4'-(2-Benzyl-benzofuran-3-yl)-3-nitro-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

Step a) 4'-(2-Benzyl-benzofuran-3-yl)-3-nitro-biphenyl-4-ol

Iron (III) nitrate nonahydrate (8.04 g, 19.9 mmol) was added to a solution of 4'-(2-benzyl-benzofuran-3-yl)-biphenyl-4-ol (6.8 g, 18.1 mmol) in absolute ethanol (80 mL), and the mixture was heated to 45 °C for 1.5 hour. The reaction mixture was cooled to room temperature and poured into HCl (0.1N) and extracted with ethyl acetate 3 times. The extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc/petroleum ether) gave the title compound as a yellow solid, mp 75 °C; MS *m/e* 420 $(M - H)^+$. Analysis for $C_{27}H_{19}NO_4 \bullet 0.5\ H_2O$: Calcd. C, 75.34; H, 4.68; N, 3.25. Found: C, 75.6; H, 4.51; N, 3.11.

Step b) 4-[4'-(2-benzyl-benzofuran-3-yl)-3-nitro-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

The title compound was prepared from 4'-(2-benzyl-benzofuran-3-yl)-3-nitro-biphenyl-4-ol and 4-chlorosulfonyl-2-hydroxy-benzoic acid, in substantially the same manner, as described in Example 1 step g, and was obtained as a yellow solid, mp 200°C; MS *m/e* 620 $(M-H)^+$;

Analysis for: $C_{34}H_{23}NO_9S$ Calc'd: C, 62.9; H, 3.54; N, 2.2 Found: C, 62.85; H, 3.9; N, 2.02

Example 8

4-[4'-(2-Benzoyl-benzofuran-3-yl)-3-nitro-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

The title compound was prepared from 4'-(2-benzoyl-benzofuran-3-yl)-3-nitro-biphenyl-4-ol and 4-chlorosulfonyl-2-hydroxy-benzoic acid, in substantially the same manner, as described in Example 1 step g, and was obtained as a yellow solid, mp 105-107 °C; MS *m/e* 683 $(M-H)^+$;

Analysis for: $C_{34}H_{21}NO_{10}S$ x .55 EtOAc Calc'd: C, 63.56; H, 3.74; N, 2.05 Found: C, 61.91; H, 3.7; N, 1.93

Example 9

4-[4'-(2-Benzoyl-benzofuran-3-yl)-3-cyclopentyl-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

The title compound was prepared from 4'-(2-benzoyl-benzofuran-3-yl)-3-cyclopentyl-biphenyl-4-ol and 4-chlorosulfonyl-2-hydroxy-benzoic acid, in substantially the same manner, as described in Example 1 step g, and was obtained as a yellow solid, mp 105-108 °C; MS *m/e* 694 $(M-H)^+$;

Analysis for: $C_{39}H_{30}O_8S$ x 0.33 EtOAc x 0.44 H_2O Calc'd: C, 69.61; H, 4.86 Found: C, 67.37; H, 4.68

Example 10

4-[4'-(2-Benzyl-4,5-dimethyl-thiophen-3-yl)-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

The title compound was prepared from 4'-(2-benzyl-4,5-dimethyl-thiophen-3-yl)-biphenyl-4-ol and 4-chlorosulfonyl-2-hydroxy-benzoic acid, in substantially the same manner, as described in Example 1 step g, and was obtained as a white solid, mp 173-175 °C; MS *m/e* 570 $(M-H)^+$;

Analysis for: $C_{32}H_{26}O_6S_2$ x 0.4 H_2O Calc'd: C, 66.51; H, 4.67 Found: C, 66.47; H, 4.55

Example 11

4-[4'-(2-Benzyl-benzo[b]thiophen-3-yl)-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

Step a) 3-(4'-Methoxy-biphenyl-4-yl)-benzo[b]thiophene

Palladium (II) acetate was added into a mixture of 3-bromo-benzo[b]-thiophene (1.4 g, 6.58 mmol), 4'-methoxy-biphenyl-4-boronic acid (1.5 g, 6.58 mmol), potassium carbonate (2.27 g, 16.45 mmol), acetone (20) and H_2O (20 mL). The reaction mixture was at 65 °C for 2h, poured into water, and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$ Evaporation and crystallization from ethyl ether/hexanes gave an off-white solid (1.76 g, 85% yield): mp 134-136; MS *m/e* 316 (M^+);

Analysis for: $C_{21}H_{16}OS$ Calc'd: C, 79.71; H, 5.10 Found: C, 78.98; H, 5.13

Step b) 4'-Benzo[b]thiophen-3-yl-biphenyl-4-ol

This compound was prepared from 3-(4'-methoxy-biphenyl-4-yl)-benzo[b]-thiophene, in substantially the same manner, as described in Example 1 step d, and was obtained as an off-white solid, mp 167-169 °C; MS *m/e* 302 (M^+);

Analysis for: $C_{20}H_{14}OS$ Calc'd: C, 79.44; H, 4.67 Found: C, 79.36; H, 4.52

Step c) [3-(4'-Hydroxy-biphenyl-4-yl)-benzo[b]thiophen-2-yl]-phenyl-methanone

This compound was prepared from 4'-benzo[b]thiophen-3-yl-biphenyl-4-ol, in substantially the same manner as described in Example 1 step e, and was obtained as a yellow solid, mp 205-207 °C; MS *m/e* 406 (M^+);

Analysis for: $C_{27}H_{18}O_2S$ Calc'd: C, 79.78; H, 4.46 Found: C, 78.95; H, 4.59

Step d) 4'-(2-Benzyl-benzo[b]thiophen-3-yl)-biphenyl-4-ol

This compound was prepared from[3-(4'-hydroxy-biphenyl-4-yl)-benzo[b]thiophen-2-yl]-phenyl-methanone, in substantially the same manner as described in Example 1 step f, and was obtained as a white solid, mp 178-180 °C; MS *m/e* 392 (M^+);

Analysis for: $C_{27}H_{20}OS$ Calc'd: C, 81.62; H, 5.14 Found: C, 81.60; H, 5.32

Step e) 4-[4'-(2-Benzyl-benzo[b]thiophen-3-yl)-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

The title compound was prepared from 4'-(2-Benzyl-benzo[b]thiophen-3-yl)-biphenyl-4-ol and 4-chlorosulfonyl-2-hydroxy-benzoic acid, in substantially the same manner, as described in Example 1 step g, and was obtained as a white solid, mp 236-238 °C; MS *m/e* 591 $(M-H)^+$;

Analysis for: $C_{34}H_{24}O_6S_2$ x 0.35 H_2O Calc'd: C, 68.17; H, 4.16; Found: C, 68.18; H, 4.44

Example 12

4-[4'-(2-Benzyl-benzo[b]thiophen-3-yl)-3-bromo-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

Step a) 4'-(2-Benzyl-benzo[b]thiophen-3-yl)-3-bromo-biphenyl-4-ol or 4'-(2-Benzyl-benzo[b]thiophen-3-yl)-3,5-dibromo-biphenyl-4-ol

Bromine (1.47 mL, 28.69 mmol) in acetic acid (50 mL) was added dropwise over a 30 minutes period into a cold (5 °C) mixture of 4'-(2-benzyl-benzo[b]thiophen-3-yl)-biphenyl-4-ol (7.5 g, 19.13 mmol), potassium acetate (18.6 g, 190.13 mmol), and acetic acid (200 mL). After the addition the mixture was poured into water, and extracted with ethyl ether. The organic extracts were washed with aqueous sodium bisulfite and dried over $MgSO_4$. Evaporation and purification by flash chromatography on silica gel (hexanes/EtAOc/CH_2Cl_2 3:1:1) gave 4'-(2-benzyl-benzo[b]thiophen-3-yl)-3-bromo-biphenyl-4-ol as a light yellow solid (2.4 g): mp 54-56 °C MS *m/e* 477 (M^+);

Analysis for: $C_{27}H_{19}BrOS$ Calc'd: C, 68.79; H, 4.06 Found: C, 68.37; H, 4.17

and 4'-(2-benzyl-benzo[b]thiophen-3-yl)-3,5-dibromo-biphenyl-4-ol as a light yellow solid (4.7 g); mp 59-61 °C; MS *m/e* 548 (M^+);

Analysis for: $C_{27}H_{18}Br_2OS$ Calc'd: C, 58.93; H, 3.30 Found: C, 59.21; H, 3.57

Step b) 4-[4'-(2-Benzyl-benzo[b]thiophen-3-yl)-3-bromo-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

The title compound was prepared from 4'-(2-benzyl-benzo[b]thiophen-3-yl)-3-bromo-biphenyl-4-ol and 4-chlorosulfonyl-2-hydroxy-benzoic acid, in substantially the same manner, as described in Example 1 step g, and was obtained as an off-white solid, mp 117-119 °C; MS *m/e* 669 $(M-H)^+$;

Analysis for: $C_{34}H_{23}BrO_6S_2$ Calc'd: C, 60.81; H, 3.45 Found: C, 60.57; H, 3.79

Example 13

4-[4'-(2-Benzyl-benzo[b]thiophen-3-yl)-3,5-dibromo-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid

The title compound was prepared from 4'-(2-benzyl-benzo[b]thiophen-3-yl)-3,5-dibromo-biphenyl-4-ol and 4-chlorosulfonyl-2-hydroxy-benzoic acid, in substantially the same manner, as described in Example 1 step g, and was obtained as white solid, mp 192-194 °C; MS *m/e* 747 $(M-H)^+$;

Analysis for: $C_{34}22_4Br_2O_6S_2$ Calc'd: C, 54.42; H, 2.95 Found: C, 55.21; H, 3.76

Example 14

2-Hydroxy-4-{3'-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazole-4-yl]-biphenyl-4-yoxysulfonyl}-benzoic acid

Step a) 1-(4-bromo-phenyl)-propanone oxime

Sodium acetate (80.0g, 976 mmol) was added into a mixture of 1(4-bromo-phenyl)-propanone (52.0 g, 244 mmol), hydroxylamine hydrochloride (50.8 g, 732.3 mmol), ethyl alcohol (500 mL) and water (100 mL). The reaction mixture was stirred at 60 ° C for 1 hour, poured into water, and extracted with ethyl ether. The organic extracts were dried over $MgSO_4$. Evaporation and crystallization from ethyl ether / hexanes gave a white solid (49.6 g, 89% yield); MS *m/e* 227(M^+); Analysis for $C_9H_{10}BrNO$: Calc'd: C, 47.39; H, 4.42; N, 6.14 Found: C, 47.42; H, 4.37; N, 5.99

Step b) 4-(4-Bromo-phenyl)-5-methyl-2-(4-trifluoromethyl-phenyl)-oxazole

Pyridine (3.55 mL, 43.86 mmol) was added into a mixture of 1-(4-bromo-phenyl)-propanone oxime (10.0g, 43.86 mmol) and toluene (20 mL). The reaction mixture was stirred for 30 minutes, and then 4-trifluoromethyl-phenyl acetyl chloride (16.27 mL, 109.6 mmol) was added dropwise. The new mixture was stirred at 100 °C for 24 hours, and then was poured into water and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography on silica gel (hexanes/EtoAc 40:1) gave a white solid (7.3 g, 43% yield): mp 82.84 °C; MS *m/e* 381 (M^+);

Analysis for: $C_{17}H_{11}BrF_3NO$ Calc'd: C, 53.43; H, 2.90; N, 3.67 Found: C, 53.47; H, 2.62; N, 3.43

Step c) 4-(4'-Methoxy-biphenyl-4-yl)-5-methyl-2-(4-trifluoromethyl-phenyl)-oxazole

4-Methoxy-benzeneboronic acid (1.44 g, 7.19 mmol) in ethyl alcohol (5 mL) was added into a mixture of 4-(4-bromo-phenyl)-5-methyl-2-(4-trifluoromethyl-

phenyl)-oxazole (2.5 g, 6.54mmol), sodium carbonate (2N, 6.5 mL), tetrakis-(triphenylphosphine)palladium(0) (0.23 g, 0.196 mmol), and toluene (200 mL). The reaction mixture was refluxed for 12 hours, cooled to room temperature, and treated with hydrogen peroxide (30%, 5 mL) for 1 hour. Then, the mixture was poured into water and extracted with ethyl acetate. The organic extracts were dried over $MgSO_4$. Evaporation and crystallization from hexanes/ethyl ether gave a white solid (2.2 g, 82% yield): mp 167-168 °C; MS *m/e* 409 (M^+);

Analysis for: $C_{24}H_{18}F_3NO_2$ Calc'd: C, 70.41; H, 4.43; N, 3.42 Found: C, 70.14; H, 4.32; N, 3.30

Step d) <u>4'-[5-Methyl-2-(4-trifluoromethyl-phenyl)-oxazole-4-yl]-biphenyl-4-ol</u>

Boron tribromide (1.0 M, 3.91 mL, 3.91 mmol) was added dropwise into a cold (-78 °C) mixture of 4-(4'-methoxy-biphenyl-4-yl)-5-methyl-2-(4-trifluoromethyl-phenyl)-oxazole (1.6 g, 3.91 mmol), and dichloromethane (20 mL). The reaction mixture was allowed to come gradually to room temperature and stirred for 10 hours. Then, the mixture was cooled to 0 °C and methyl alcohol (5 mL) was added dropwise. After stirring for 10 minutes the mixture was poured into water and extracted with ethyl ether. The organic extracts were dried over $MgSO_4$. Evaporation and crystallization from ethyl ether/hexanes gave an off-white solid (1.4 g, 90% yield): mp 189-191; MS *m/e* 396 $(M+H)^+$;

Analysis for: $C_{23}H_{16}F_3NO_2$ x 0.3 H_2O Calc'd: C, 68.92; H, 4.17; N, 3.50 Found: C, 68.97; H, 4.23; N, 3.33

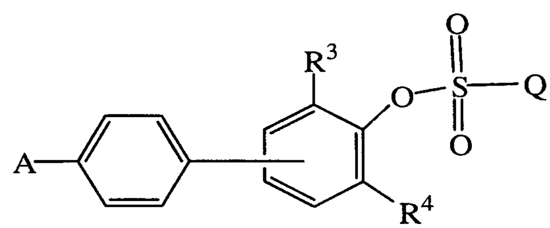
Step e) <u>2-Hydroxy-4-{3'-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazole-4-yl]-biphenyl-4-yloxysulfonyl}-benzoic acid</u>

This compound was prepared from 4'-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazole-4-yl]-biphenyl-4-ol and 4-chlorosulfonyl-2-hydroxy-benzoic acid, in substantially the same manner, as described in Example 1 step g, and was obtained as white solid, mp 216-218 °C; MS *m/e* 594 $(M-H)^+$;

Analysis for: $C_{30}H_{20}F_3NO_7S$ Calc'd: C, 60.50; H, 3.38; N, 2.35 Found: C, 60.11; H, 3.28; N, 2.29

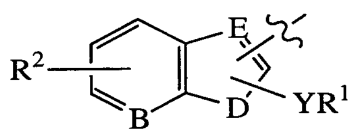
WHAT IS CLAIMED IS:

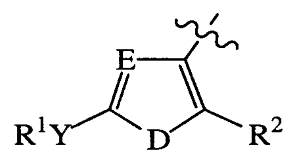
1. A compound of formula I having the structure



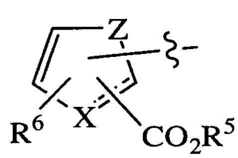
I

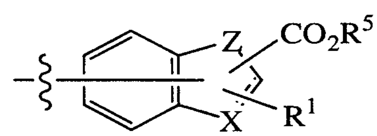
wherein

A is 

or 

;

Q is 

or 

;

B is carbon or nitrogen;

D is oxygen, sulfur, or nitrogen;

E is carbon or nitrogen;

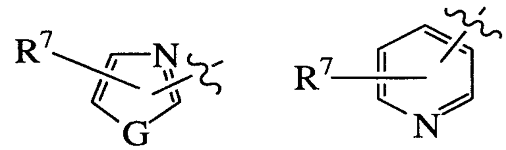
X is carbon, nitrogen, oxygen, or sulfur;

Y is a bond, methylene, C(O), or CH(OH);

Z is CH=CH, nitrogen, oxygen, or sulfur;

the dashed line of Q represents an optional double bond;

R^1 is alkyl of 1 to 12 carbons, aryl of 6-10 carbon atoms, aralkyl of 7-15 carbon atoms, halogen, trifluoromethyl, alkoxy of 1-6 carbon atoms, Het-alkyl wherein the alkyl moiety contains 1-6 carbon atoms, or aryl of 6-10 carbon atoms mono-, di-, or tri-substituted with trifluoromethyl, alkyl of 1-6 carbon atoms or, alkoxy of 1-6 carbon atoms;

Het is  ;

R^7 is alkylene of 1 to 3 carbon atoms,

G is oxygen, sulfur or nitrogen;

R^2 is hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, or trifluoromethyl;

R^3 and R^4 are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, aryl of 6-10 carbon atoms, halogen, trifluoromethyl, alkoxy of 1-6 carbon atoms, aryl of 6-10 carbon atoms mono-, di-, or tri-substituted with trifluoromethyl, alkyl of 1-6 carbon atoms or, alkoxy of 1-6 carbon atoms, nitro, alkylsulfamide; arylsulfamide, cycloalkyl of 3-8 carbon atoms or a heterocyclic ring containing 5 to ring 7 atom rings having 1 to 3 heteroatoms selected from oxygen, nitrogen, or sulfur;

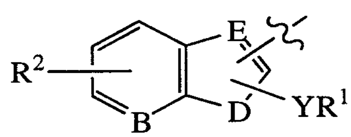
R^5 is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6-10 carbon atoms, or aralkyl of 7-15 carbon atoms;

R^6 is hydrogen, $-OR^5$, or $-OCOR^5$;

with the proviso that when R^1 is halogen, Y is a bond,

or a pharmaceutically acceptable salt thereof.

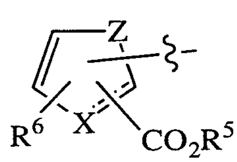
2. The compound according to claim 1, wherein

A is  ;

B is -CH-;

E is -CH-;

D is oxygen or suflur;

Q is  ;

Z is CH=CH;

X is carbon;

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 which is 4-[4'-(2-benzyl-benzofuran-3-yl)-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1 which is 5-[4'-(2-benzyl-benzofuran-3-yl)-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1 which is 4-[4'-(2-benzyl-benzofuran-3-yl)-biphenyl-4-yloxysulfonyl]-benzoic acid or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1 which is 3-[4'-(2-benzyl-benzofuran-3-yl)-biphenyl-4-yloxysulfonyl]-benzoic acid or a pharmaceutically acceptable salt thereof.

7. The compound of claim 1 which is 4-[4'-(2-benzyl-benzo[b]thiopen-3-yl)-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid or a pharmaceutically acceptable salt thereof.

8. The compound of claim 1 which is 4-[4'-(2-benzyl-benzo[b]thiopen-3-yl)-3-bromo-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid or a pharmaceutically acceptable salt thereof.

9. The compound of claim 1 which is 4-[4'-(2-benzyl-benzo[b]thiopen-3-yl)-3,5-dibromo-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid or a pharmaceutically acceptable salt thereof.

10. The compound of claim 1 which is 4-[4'-(2-benzyl-benzofuran -3-yl)-3,5-dimethyl-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1 which is 4-[4'-(2-benzoyl-benzofuran-3-yl)-3-nitro-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid or a pharmaceutically acceptable salt thereof.

12. The compound of claim 1 which is 4-[4'-(2-benzyl-benzofuran-3-yl)-3-bromo-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid or a pharmaceutically acceptable salt thereof.

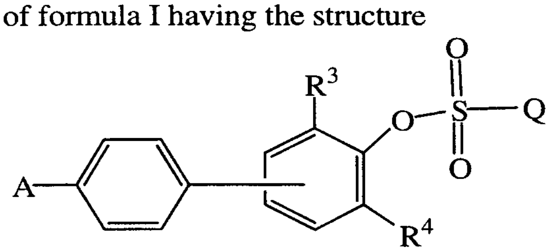
13. The compound of claim 1 which is 4-[4'-(2-benzoyl-benzofuran-3-yl)-3-cyclopentyl-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid or a pharmaceutically acceptable salt thereof.

14. The compound of claim 1 which is 4-[4'-(2-benzyl-4,5-dimethyl-thiopen-3-yl)-3-bromo-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid or a pharmaceutically acceptable salt thereof.

15. The compound of claim 1 which is 4-(4'-benzofuran-3-yl)-biphenyl-4-yloxysulfonyl]-2-hydroxy-benzoic acid or a pharmaceutically acceptable salt thereof.

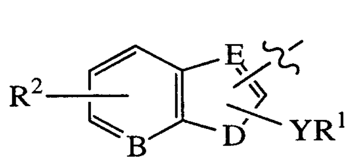
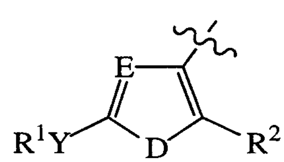
16. The compound of claim 1 which is 2-hydroxy-4-{3'-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-yl]-biphenyl-4-yloxysulfonyl}-benzoic acid or a pharmaceutically acceptable salt thereof.

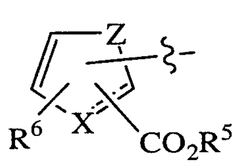
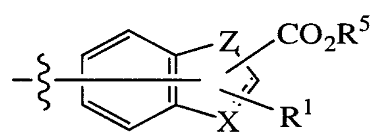
17. A method of treating metabolic disorders mediated by insulin resistance or hyperglycemia in a mammal in need thereof which comprises administering to said mammal, a compound of formula I having the structure



I

wherein

A is  or  ;

Q is  or  ;

B is carbon or nitrogen;

D is oxygen, sulfur, or nitrogen;

E is carbon or nitrogen;

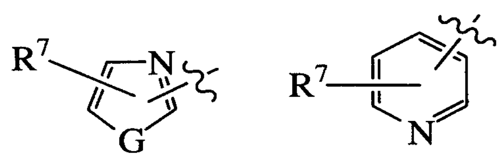
X is carbon, nitrogen, oxygen, or sulfur;

Y is a bond, methylene, C(O), or CH(OH);

Z is CH=CH, nitrogen, oxygen, or sulfur;

the dashed line of Q represents an optional double bond;

R^1 is alkyl of 1 to 12 carbons, aryl of 6-10 carbon atoms, aralkyl of 7-15 carbon atoms, halogen, trifluoromethyl, alkoxy of 1-6 carbon atoms, Het-alkyl wherein the alkyl moiety contains 1-6 carbon atoms, or aryl of 6-10 carbon atoms mono-, di-, or tri-substituted with trifluoromethyl, alkyl of 1-6 carbon atoms or, alkoxy of 1-6 carbon atoms;

Het is  ;

R^7 is alkylene of 1 to 3 carbon atoms,

G is oxygen, sulfur or nitrogen;

R^2 is hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, or trifluoromethyl;

R^3 and R^4 are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, aryl of 6-10 carbon atoms, halogen, trifluoromethyl, alkoxy of 1-6 carbon atoms, aryl of 6-10 carbon atoms mono-, di-, or tri-substituted with trifluoromethyl, alkyl of 1-6 carbon atoms or, alkoxy of 1-6 carbon atoms, nitro, alkylsulfamide; arylsulfamide, cycloalkyl of 3-8 carbon atoms or a heterocyclic ring containing 5 to ring 7 atom rings having 1 to 3 heteroatoms selected from oxygen, nitrogen, or sulfur;

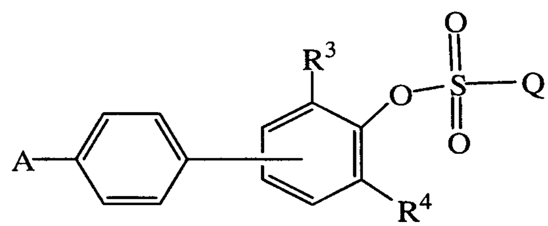
R^5 is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6-10 carbon atoms, or aralkyl of 7-15 carbon atoms;

R^6 is hydrogen, $-OR^5$, or $-OCOR^5$;

with the proviso that when R^1 is halogen, Y is a bond,

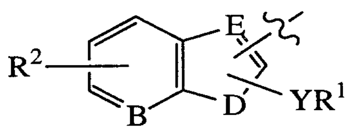
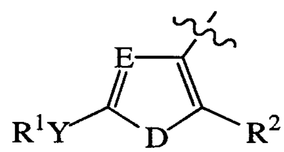
or a pharmaceutically acceptable salt thereof.

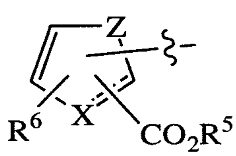
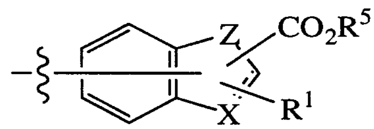
18. A method of treating or inhibiting type II diabetes in a mammal in need thereof which comprises administering to said mammal, a compound of formula I having the structure



I

wherein

A is  or  ;

Q is  or  ;

B is carbon or nitrogen;

D is oxygen, sulfur, or nitrogen;

E is carbon or nitrogen;

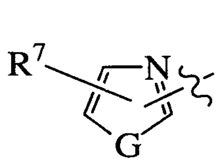
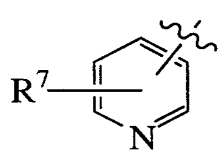
X is carbon, nitrogen, oxygen, or sulfur;

Y is a bond, methylene, C(O), or CH(OH);

Z is CH=CH, nitrogen, oxygen, or sulfur;

the dashed line of Q represents an optional double bond;

R^1 is alkyl of 1 to 12 carbons, aryl of 6-10 carbon atoms, aralkyl of 7-15 carbon atoms, halogen, trifluoromethyl, alkoxy of 1-6 carbon atoms, Het-alkyl wherein the alkyl moiety contains 1-6 carbon atoms, or aryl of 6-10 carbon atoms mono-, di-, or tri-substituted with trifluoromethyl, alkyl of 1-6 carbon atoms or, alkoxy of 1-6 carbon atoms;

Het is   ;

R^7 is alkylene of 1 to 3 carbon atoms,

G is oxygen, sulfur or nitrogen;

R^2 is hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, or trifluoromethyl;

R^3 and R^4 are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, aryl of 6-10 carbon atoms, halogen, trifluoromethyl, alkoxy of 1-6 carbon atoms, aryl of 6-10 carbon atoms mono-, di-, or tri-substituted with trifluoromethyl, alkyl of 1-6 carbon atoms or, alkoxy of 1-6 carbon atoms, nitro, alkylsulfamide; arylsulfamide, cycloalkyl of 3-8 carbon atoms or a heterocyclic ring containing 5 to ring 7 atom rings having 1 to 3 heteroatoms selected from oxygen, nitrogen, or sulfur;

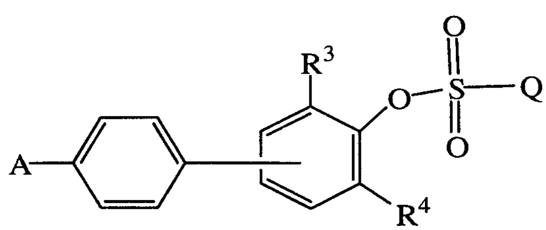
R^5 is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6-10 carbon atoms, or aralkyl of 7-15 carbon atoms;

R^6 is hydrogen, -OR^5, or -$OCOR^5$;

with the proviso that when R^1 is halogen, Y is a bond,

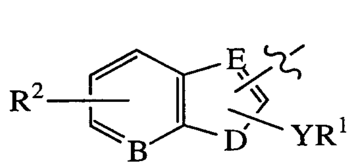
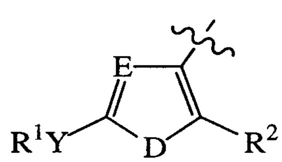
or a pharmaceutically acceptable salt thereof.

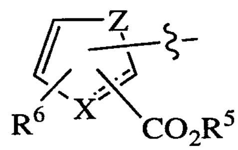
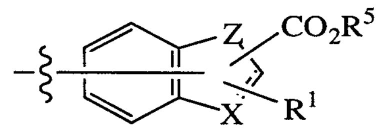
19. A method of modulating glucose levels in a mammal in need thereof which comprises administering to said mammal, a compound of formula I having the structure



I

wherein

A is  or  ;

Q is  or  ;

B is carbon or nitrogen;

D is oxygen, sulfur, or nitrogen;

E is carbon or nitrogen;

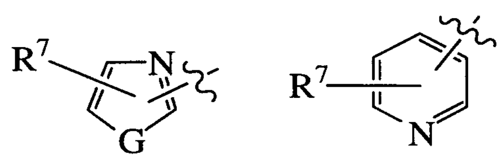
X is carbon, nitrogen, oxygen, or sulfur;

Y is a bond, methylene, C(O), or CH(OH);

Z is CH=CH, nitrogen, oxygen, or sulfur;

the dashed line of Q represents an optional double bond;

R^1 is alkyl of 1 to 12 carbons, aryl of 6-10 carbon atoms, aralkyl of 7-15 carbon atoms, halogen, trifluoromethyl, alkoxy of 1-6 carbon atoms, Het-alkyl wherein the alkyl moiety contains 1-6 carbon atoms, or aryl of 6-10 carbon atoms mono-, di-, or tri-substituted with trifluoromethyl, alkyl of 1-6 carbon atoms or, alkoxy of 1-6 carbon atoms;

Het is  ;

R^7 is alkylene of 1 to 3 carbon atoms,

G is oxygen, sulfur or nitrogen;

R^2 is hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, or trifluoromethyl;

R^3 and R^4 are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, aryl of 6-10 carbon atoms, halogen, trifluoromethyl, alkoxy of 1-6 carbon atoms, aryl of 6-10 carbon atoms mono-, di-, or tri-substituted with trifluoromethyl, alkyl of 1-6 carbon atoms or, alkoxy of 1-6 carbon atoms, nitro, alkylsulfamide; arylsulfamide, cycloalkyl of 3-8 carbon atoms or a heterocyclic ring containing 5 to ring 7 atom rings having 1 to 3 heteroatoms selected from oxygen, nitrogen, or sulfur;

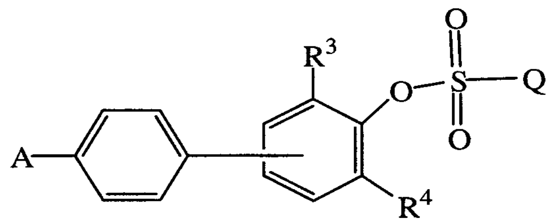
R^5 is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6-10 carbon atoms, or aralkyl of 7-15 carbon atoms;

R^6 is hydrogen, $-OR^5$, or $-OCOR^5$;

with the proviso that when R^1 is halogen, Y is a bond,

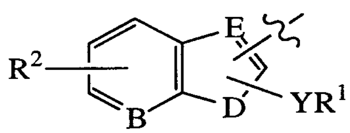
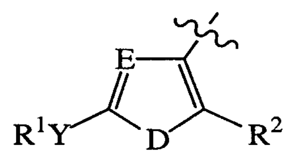
or a pharmaceutically acceptable salt thereof.

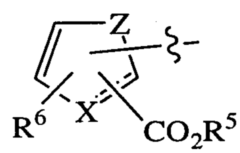
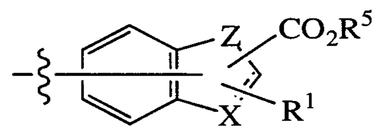
20. A pharmaceutical composition which comprises a compound of formula I having the structure



I

wherein

A is  or  ;

Q is  or  ;

B is carbon or nitrogen;

D is oxygen, sulfur, or nitrogen;

E is carbon or nitrogen;

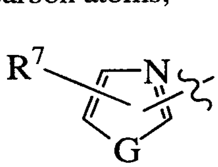
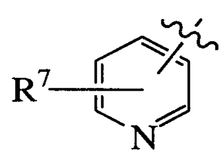
X is carbon, nitrogen, oxygen, or sulfur;

Y is a bond, methylene, C(O), or CH(OH);

Z is CH=CH, nitrogen, oxygen, or sulfur;

the dashed line of Q represents an optional double bond;

R^1 is alkyl of 1 to 12 carbons, aryl of 6-10 carbon atoms, aralkyl of 7-15 carbon atoms, halogen, trifluoromethyl, alkoxy of 1-6 carbon atoms, Het-alkyl wherein the alkyl moiety contains 1-6 carbon atoms, or aryl of 6-10 carbon atoms mono-, di-, or tri-substituted with trifluoromethyl, alkyl of 1-6 carbon atoms or, alkoxy of 1-6 carbon atoms;

Het is   ;

R^7 is alkylene of 1 to 3 carbon atoms,

G is oxygen, sulfur or nitrogen;

R^2 is hydrogen, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, or trifluoromethyl;

R^3 and R^4 are each, independently, hydrogen, halogen, alkyl of 1-6 carbon atoms, aryl of 6-10 carbon atoms, halogen, trifluoromethyl, alkoxy of 1-6 carbon atoms, aryl of 6-10 carbon atoms mono-, di-, or tri-substituted with trifluoromethyl, alkyl of 1-6 carbon atoms or, alkoxy of 1-6 carbon atoms, nitro, alkylsulfamide; arylsulfamide, cycloalkyl of 3-8 carbon atoms or a heterocyclic ring containing 5 to ring 7 atom rings having 1 to 3 heteroatoms selected from oxygen, nitrogen, or sulfur;

R^5 is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6-10 carbon atoms, or aralkyl of 7-15 carbon atoms;

R^6 is hydrogen, $-OR^5$, or $-OCOR^5$;

with the proviso that when R^1 is halogen, Y is a bond,

or a pharmaceutically acceptable salt thereof, and a pharmaceutical carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/10213

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D307/80 C07D333/16 C07D333/56 C07D263/32 A61K31/34
A61K31/38 A61K31/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 00137 A (DOMINIANNI SAMUEL J ;WINNEROSKI LEONARD L JR (US); FAUL MARGARET M) 8 January 1998 (1998-01-08) claims 1,6,21,24; examples	1,17-20
A	EP 0 275 024 A (BOEHRINGER MANNHEIM GMBH) 20 July 1988 (1988-07-20) the whole document	1,17-20
A	EP 0 092 239 A (TAKEDA CHEMICAL INDUSTRIES LTD) 26 October 1983 (1983-10-26) the whole document	1,17-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 September 1999	20/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bosma, P

1

INTERNATIONAL SEARCH REPORT

national application No.

PCT/US 99/10213

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 17-19
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/10213

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9800137 A	08-01-1998	AU 3719997 A	21-01-1998
		EP 0925063 A	30-06-1999
EP 0275024 A	20-07-1988	DE 3700732 A	21-07-1988
		AT 66920 T	15-09-1991
		DE 3864524 A	10-10-1991
		JP 63174949 A	19-07-1988
		US 4833161 A	23-05-1989
EP 0092239 A	26-10-1983	JP 58183676 A	26-10-1983
		AU 1355283 A	27-10-1983
		CA 1195985 A	29-10-1985
		DK 172183 A	20-10-1983
		FI 831253 A	20-10-1983
		GR 79251 A	22-10-1984
		PT 76563 A,B	01-05-1983
		US 4596816 A	24-06-1986
		ZA 8302657 A	25-01-1984